REMARKS

Status of the Claims

Claims 5, 6, 20 and 21 are pending as shown above. As claim 21 is not subject to the sole remaining rejection (under 35 U.S.C. § 103(a)), it appears to be in condition for allowance if rewritten in independent form.

Rejections Withdrawn

The rejections under 35 U.S.C. § 112, 1st paragraph and 35 U.S.C. § 102 have been withdrawn. (Office Action, page 2). In addition, the rejections under 35 U.S.C. § 103 based on Eisenberg were not reiterated and are therefore considered withdrawn.

35 U.S.C. 103(a)

The rejection of previously pending claims 5, 6 and 20 under 35 U.S.C. § 103(a) as allegedly obvious over Pomerantz (1988) *Biochemistry* 37(4):965-970 (hereinafter "Pomerantz") in view of Krylov et al. (1994) *EMBO J.* 13(12):2849-2861 (hereinafter "Krylov") was reiterated by the Examiner. (Office Action, pages 2-9). Pomerantz was cited for allegedly disclosing a zinc finger protein fused to a naturally occurring dimerization domain extracted from the GAL4 protein and for suggesting the use of non-naturally occurring dimerization domains. *Id.* Krylov, reference 19 of Pomerantz, was cited for demonstrating that non-naturally occurring peptide linkers could be utilized to complex zinc finger proteins. *Id.*

In response to Applicants arguments, it was asserted that Pomerantz teaches "fusion" with short peptide linkers for covalent linkages, which makes it obvious to use such linkers for non-covalent linkages. (Office Action, pages 5-7). With regard to the argument that Krylov fails to teach dimerization domains under 30 amino acids, the Examiner asserted that "the selection of 30 or fewer amino acids in length from random peptide libraries is not commensurate in scope with the claims" and that Krylov discloses that leucine zippers include 4 heptad repeats (Office Action, pages 8-9).

To reiterate, the pending claims are drawn to a complex comprising two fusion proteins. Each fusion protein comprises a zinc finger protein and a non-naturally occurring peptide linker that forms a dimer (via a non-covalent link) with the corresponding non-naturally occurring

peptide linker on a separate fusion protein. In addition, each peptide linker is 30 or fewer amino acids in length. The claims are composition claims and, therefore, contrary to the Examiner's assertion, the pending composition claims properly include a size limitation on the length of the peptide linker without any recitation of a process step regarding selection of the peptide linker from a randomized library.

For the reasons of record and reiterated herein, neither Pomerantz nor Krylov teach or suggest non-covalent linkage of 2 fusion proteins using two non-naturally occurring linker peptides less than 30 amino acids in length. Rather, Pomerantz and Krylov are cited for teaching much longer dimerization peptides that are either naturally occurring Gal4 domains of 59 amino acids in length or mutated leucine zipper-containing proteins of 80 amino acids in length. Thus, the rejection is premised on the assertion that references alleged disclosure that covalent linkage using a single peptide linker of 30 amino acids or less is somehow predictive of the claimed non-covalently molecules.

However, the fact remains that the references and art as a whole teach that covalent peptide linkers are completely different than non-covalent dimerization peptides. Hence, there is no suggestion and nothing predictable about using short single peptides used for covalent linkage as dimerizing, non-covalent linkages. Indeed, Pomerantz clearly teaches that covalent linkage and non-covalent dimerization are completely different strategies (Pomerantz, page 966, left column, emphasis added):

> Dimer formation, frequently employed by natural DNA-binding proteins to enhance the affinity and specificity of recognition provides **another** attractive design strategy. ... Design strategies that employ dimerization also may provide a **useful alternative to the covalent linkage** of multiple DNA-binding domains. Large covalent assemblies might have higher absolute affinity for nonspecific DNA sites and might become kinetically trapped at inappropriate sites in the genome. Dimerization provides **an alterative way** of bringing multiple domains together as a functional recognition unit.

Clearly, this is not in any way a suggestion to use the short covalent peptides for dimerization. Nor does it in any way establish that peptides of 30 amino acids or less were known by the skilled artisan to be predictably used as either covalent or non-covalent linkers.

In further support of the assertion that covalent and non-covalent linkers were somehow considered predictably interchangeable at the time of filing, the Examiner points to passages from the specification which are alleged to show "art-recognized" predictability of using short peptides as covalent or as non-covalent linkers. (Office Action, page 6). However, any teachings of the as-filed specification regarding the claimed short dimerizing peptides cannot be used against Applicants as this is clearly impermissible hindsight reconstruction based on Applicants' first showing that shorter, non-naturally occurring dimerizing peptides are indeed functional. The passages of the specification actually show that it was unpredictable to use shorter linkers for dimerization.

For its part, Krylov is admittedly silent as to covalent linkages. In addition, Krylov fails to teach or suggest dimerizing proteins of 30 or fewer amino acids. The assertion that because Krylov teaches that the leucine zipper domain of the dimerization domain is made up of 4 heptad repeats does not in any way teach or suggest peptides as claimed. First, Krylov is clear that the leucine zipper domain of their protein is made up of 4 heptads and 3 amino acids N-terminal to the first heptad (ITI in Figure 1B) and at least 1 amino acid C-terminal to fourth heptad (I in Figure 1B). Indeed, the fourth heptad is actually octad as it contains a second g residue. (I in Figure 1B). Thus, Krylov teaches that the leucine zipper domain of VBP contains 32 amino acid residues, which does not fall within the scope of the claims.

Furthermore, there is absolutely no suggestion in Kryrlov that the leucine zipper domain zipper portion would, in isolation from the remaining 50 amino acids of VBP, act as a dimerization peptide. Simply put, Krylov contains absolutely no teachings regarding using fragments of the naturally occurring 80-amino acid long VBP protein.

In sum, because each reference teaches dimerization peptides of greater than 30 amino acids in length, and because Pomerantz (and the art as a whole) fails to show predictable use of covalent linkers for dimerization, there is no combination of Krylov and Pomerantz that would result in the claimed complexes that include peptides of 30 or fewer amino acids in length.

For all of the aforementioned reasons, the rejection of claims 5, 6 and 20 under 35 U.S.C. § 103(a) should be withdrawn.

CONCLUSION

Applicants believe that the claimed subject matter is now in condition for allowance and early notification to that effect is respectfully requested. If any issues remain to be addressed, the Examiner is encouraged to telephone the undersigned.

Please address all correspondence to the undersigned.

Respectfully submitted,

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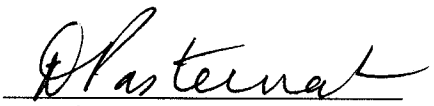
By: 

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